

## Amendments to the Specification

Please replace indicated paragraphs with the following:

[0052] For example, octapeptides (P<sub>4</sub>-P'<sub>4</sub>) for MMP 2 and MMP 9 have been identified (see Table 1), which octapeptides simulate the cleavage sequence of the collagen chain and are cleaved with particular efficiency by MMP 2 and 9 (in what follows, amino acids are abbreviated in accordance with the international three-letter code):

Table 1:

Peptide							
P <sub>4</sub>	P <sub>3</sub>	P <sub>2</sub>	P <sub>1</sub>	P' <sub>1</sub>	P' <sub>2</sub>	P' <sub>3</sub>	P' <sub>4</sub>
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Gly-Pro-Leu-Gly--Ile-Ala-Gly-Gln				<b><u>SEQ. ID No. 1</u></b>			
Gly-Pro-Gln-Gly--Ile-Trp-Gly-Gln				<b><u>SEQ. ID No. 2</u></b>			

(Netzel-Arnett et al., *Biochemistry* 32, 1993, 6427-6432)

[0054] Furthermore, in the case of cathepsin B, substrate-specific peptides are known with the sequence

-Gly-Phe-Leu-Gly- **SEQ. ID No. 3**

-Gly-Phe-Ala-Leu- **SEQ. ID No. 4**

-Ala-Leu-Ala-Leu- **SEQ. ID No. 5**

-Arg-Arg- or -Phe-Lys-

Werle, B., Ebert, E., Klein, W., and Spiess, E. (1995), *Biol. Chem. Hoppe-Seyler* 376, 157-164; Ulrich, B., Spiess, E., Schwartz-Albiez, R., and Ebert, W. (1995), *Biol. Chem. Hoppe-Seyler* 376, 404-414).

**[0055]** The peptide sequence that contains intended peptide cleavage points relevant for the target enzyme can also be constructed such that the intended peptide cleavage point is repeated a plurality of times, for example by: -Gly-Pro-Leu-Gly--Ile-Ala-Gly-Gln-Gly-Pro-Leu-Gly--Ile-Ala-Gly-Gln **SEQ ID No. 6**

or

-Phe-Lys-Phe-Lys-Phe-Lys-Phe-Lys-Phe-Lys-Phe-Lys- **SEQ. ID No. 7**

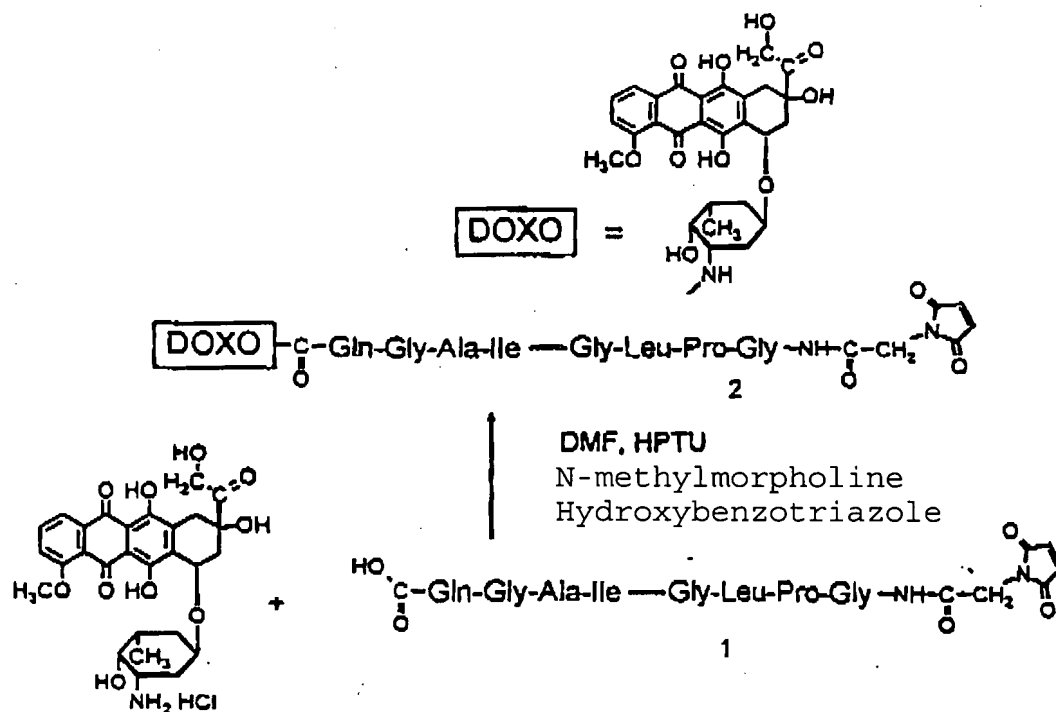
or a repetitive peptide sequence can be integrated that increases the distance between the thiol-binding group and the relevant intended peptide cleavage point, as for example by:

-(Gly)<sub>n</sub>-Phe-Lys-Phe-Lys- **SEQ ID No. 8**

with, preferably,  $n = 2$  to 20, more preferably  $n \leq 12$ .

**[0073]** Fig. 2 shows HPLC chromatograms (gel chromatography, Biosil 250 SEC column, Biorad) of a conjugate according to the invention (HSA-Cys<sup>34</sup>-2), which is cleavable by the matrix metalloprotease MMP 9. The absorption at 495 nm is also plotted versus the retention time in min. (A) Chromatogram of the conjugate HSA-Cys<sup>34</sup>-2 before incubation with MMP 9 ( $t = 0$ ). (B) Chromatogram of the conjugate HSA-Cys<sup>34</sup>-2 after incubation with MMP 9 for 30 min ( $t = 30$  min) and also showing a peak for fragment DOXO-Gln-Gly-Ala-Iic **SEQ ID No. 9**.

[0083] The doxorubicin-maleinimide-peptide derivative (2) was prepared in accordance with the following reaction equation:



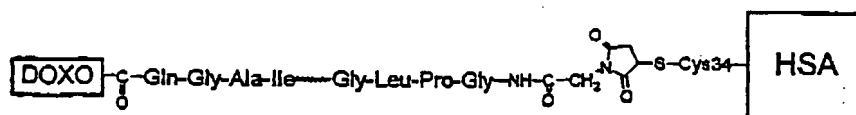
SEQ. ID No. 9

[0084] Here the octapeptide

Gln-Gly-Ala-Ile-Gly-Leu-Pro-Gly SEQ. ID No. 9

derivatized with maleinimidoglycine 1 (Mr 848, prepared by solid-phase synthesis by Bachem AG, Switzerland) was reacted with doxorubicin according to the following method:

[0086] 3.0 mL of an HSA test portion treated with DTT (sulfhydryl content of 0.95 per HSA molecule, content of HS groups 1000  $\mu$ M) was added to a solution of 2 (Mr 1374) in DMF (5.1 mg dissolved in 250  $\mu$ L of DMF), and the reaction solution, sealed, was shaken for 30 min. The product albumin-doxorubicin conjugate was isolated using a Sephacryl® HR100 column (2.0 cm x 20 cm). In this way, the albumin conjugate (designated HSA-Cys<sup>34</sup>-2 in what follows) of the following structure was isolated (exhaustion factor approximately 0.9):



HAS = human serum albumin

SEQ. ID No. 9.

[0087] The peptide sequence Gln-Gly-Ala-Ile-Gly-Leu-Pro-Gly SEQ. ID No. 9

is recognized by the matrix metalloprotease MMP 9 and cleaved between isoleucine and glycine. This was shown by the following experiment: 200  $\mu$ L of a 100  $\mu$ M solution of HSA-Cys<sup>34</sup>-2 was incubated for 30 minutes at 37 °C with trypsin/aprotinine-activated MMP 9 (2 mU, from Calbiochem, Germany). The liberation of DOXO-Gln-Gly-Ala-Ile due to cleavage with MMP 9 was confirmed by HPLC gel chromatography (Biosil 250 SEC column from Biorad, detection at  $\lambda$  = 495 nm) before incubation (t = 0, compare Fig. 2A) and after an incubation time of 30 minutes with activated MMP 9 (t = 30, compare Fig. 2B).

Applicant is supplying a clear copy of the structure as requested by the Examiner (attached at the end of this paper identified as page 25).